The Metabolic Syndrome: Overeating, Inactivity, Poor Compliance or 'Dud' Advice?

J.R. Petrie*[1], S.J. Cleland[1], M. Small[2]

[1]*University Department of Medicine and Therapeutics, Western Infirmary, Glasgow*
[2]*Diabetes Centre, Gartnavel General Hospital, West Glasgow Hospitals University NHS Trust, Glasgow*

Death from myocardial infarction was a rare clinical entity at the beginning of this century, but with an ageing population it is poised to become the most common cause of death worldwide.[1] Ample epidemiological evidence confirms the clinical impression that cardiovascular risk factors—hypertension, glucose intolerance, dyslipidaemia, obesity—tend to 'cluster' in individual patients.[2] This metabolic syndrome, or 'Syndrome X', which is thought to be underpinned by decreased insulin sensitivity, was first described in 1966 by Camus[3] and popularized by Reaven in 1988.[4] The enthusiasm and interest generated have led to the elucidation of some details concerning the pathogenesis of insulin resistance and coronary artery disease but have done little to change treatments or outcomes. Meanwhile, a global epidemic of Type 2 diabetes mellitus is said to be on the horizon[5] and it has been calculated that by the year 2230, 100 % of the adult United States population will be obese.[6] **© 1998 John Wiley & Sons, Ltd.**

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As we sit daily in our consulting rooms facing overweight, hypertensive, dyslipidaemic individuals with incipient diabetes and cardiovascular disease, what can we offer? Of all interventions, stopping smoking results in the largest reduction in coronary risk,[7] but methods for achieving this goal are under-researched. We almost routinely advise weight loss by diet but, despite occasional anecdotal successes, available evidence confirms that adults only rarely achieve sustained weight loss.[8] Similarly, routine (i.e. non-study) dietary intervention for dyslipidaemia is disappointing with, on average, only a 2–4 % fall in total cholesterol.[9] Much obesity is due to low energy expenditure rather than overeating and therefore we complement our dietary advice by encouraging exercise. Physical training has been shown to improve insulin sensitivity in both diabetic and non-diabetic subjects and, if sustained, may be of benefit in achieving weight loss and blood pressure reduction.[10] However, obese individuals tend to overestimate the amount of exercise performed and underestimate the amount of food ingested.[11] In addition, long-term participation even in supervized exercise-training programmes is usually poor, with withdrawal rates of more than 50 %.[10]

In view of the lacklustre track-record of lifestyle or so-called 'non-pharmacological' interventions in patients with the metabolic syndrome, we are tempted to reach for our prescription pads in order to treat individual features of the syndrome. Indeed, aspirin,[12] statins,[13,14] and antihypertensive agents[15] are the best validated agents for primary prevention of coronary artery disease and are likely to be even more effective in patients with frank diabetes.[7] In a therapeutic context, the concept of a metabolic 'syndrome' has been somewhat redundant as any effects of these agents on insulin resistance are unlikely to be clinically important. Direct targeting of obesity using appetite suppressant drugs (e.g. dexfenfluramine) showed initial promise in terms of weight loss, blood pressure reduction, cholesterol and glycaemia[16] but has now been abandoned owing to an excess of serious valvular heart disease. In addition, thiazolidinediones, which last year were the first peripheral insulin-sensitizing agents to reach the market,[17] were swiftly withdrawn owing to cases of fatal and non-fatal hepatic damage.

Lucky the patient who is 'non-compliant'! With the therapeutic armamentarium so poorly stocked, it may be time for a rethink of tactics, bearing in mind that Type 2 diabetes is dominant in a world of calorie excess but rare in physically active populations and those deprived of access to a lavish food supply.[18] Most of us who live in industralized parts of the world enjoy a continually improving standard of living; the upsurge in incidence of glucose intolerance appears to be coincident with globalization of the 'Western' lifestyle.[5] Experience has shown that those who find themselves in less favourable (geographical or social) circumstances are only too swift to adopt both the advantages and disadvantages of a sedentary and calorie-rich existence when the opportunity presents.

* Correspondence to: Dr John Petrie, University Department of Medicine and Therapeutics, Western Infirmary, Glasgow G11 6NT, UK

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While it would appear that the process of 'coca-colonization' or 'New World Syndrome'[19,20] may be responsible for burgeoning rates of glucose intolerance and cardiovascular disease worldwide (including the former USSR), studies conducted on the Aborigines from northern and central Australia provide a well-defined paradigm of the effects of lifestyle on risk factors for cardiovascular disease.[21] When such individuals abandon their traditional hunter-gatherer lifestyle (usually by migration to cities), they become obese, diabetic, hypertensive and hypertriglyceridaemic. Even very temporary reversion to their traditional way of life results in improvements in all of these parameters.[21] It is speculated that insulin resistance selective for carbohydrate metabolism has favoured the survival of such populations in their traditional way of life, in which occasional feasts are interspersed with frequent famines. It has been proposed that such a 'thrifty' metabolism or genotype[22] may allow post-prandial hyperinsulinaemia to exert powerful anabolic effects on lipid and protein metabolism without causing hypoglycaemia. Fuel is therefore stored for times when calories are scarce. Although the hypothesis remains controversial with regard to insulin resistance,[23] it provides an explanation of the selection pressures for a genotype predisposing to insulin resistance and obesity.

Current opinion is that there may be up to 20 human genes responsible for susceptibility to a positive energy balance and enhanced fat storage.[24] Still more loci may be involved in determining susceptibility to β-cell dysfunction. In conditions of plenty, the amount of energy expended and the quantity of calories ingested become critical. The individual who develops insulin resistance and multiple cardiovascular risk factors may be thought of as one who has too many thrifty ('Aborigine') genes than required for his or her lifestyle. In addition, the intra-uterine environment may exert as-yet poorly understood but powerful non-genetic effects on future adult cardiovascular disease (the 'thrifty phenotype').[25] Although the mechanisms underlying decreased insulin sensitivity and by which insulin resistance results in premature atherosclerosis remain poorly understood, current knowledge is sufficient (in theory at least) to allow prevention of many cases of metabolic syndrome, Type 2 diabetes and coronary artery disease.

The primary care physician knows only too well that the habits of a lifetime are hard to change. Little short of a complete reversal in public attitudes to food and exercise is necessary in affluent societies if current trends in the incidence of metabolic and cardiovascular disease are to be reversed. The failure to date of non-pharmacological interventions to deliver may be a result of their not yet having properly been tried. The public health challenge is to devise strategies by which individuals can easily select the correct diet and exercise regimen for their genetic make-up. It has been suggested that highly motivated general practitioners may be able to facilitate by organizing and encouraging community-based exercise programmes, but this is unlikely to be a priority for most doctors in their high pressure work environment. Ensuring that proven primary prevention measures (stopping smoking, aspirin, cholesterol-lowering and antihypertensives) are implemented in all patients who will benefit must be a priority. However, if real prevention is to be achieved, more direct measures (perhaps including collaboration with the food industry and an expansion of the role of physical exercise in schools/workplaces) will also be required.

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